A Case of Late Hodgkin's Disease (Lymphoma Granulomatosum),

With Remarks on Various Cases Presenting the Clinical Picture of Splenic Anemia (Banti's Disease).

BY

F. PARKES WEBER, M.D., F.R.C.P.,

PHYSICIAN TO THE GERMAN HOSPITAL, LONDON.

FROM THE

AMERICAN JOURNAL OF THE MEDICAL SCIENCES

OCTOBER, 1911

Extracted from the American Journal of the Medical Sciences, October, 1911

A CASE OF LATE HODGKIN'S DISEASE (LYMPHOMA GRANULOMATOSUM), WITH REMARKS ON VARIOUS CASES PRESENTING THE CLINICAL PICTURE OF SPLENIC ANEMIA (BANTI'S DISEASE).[1]

By F. Parkes Weber, M.D., F.R.C.P.,

PHYSICIAN TO THE GERMAN HOSPITAL, LONDON.

The patient, H. A., aged twenty-seven years, a German hairdresser in London, was admitted to the German Hospital, on September 29, 1910. Though I saw him once, myself, in February, 1909, I am chiefly indebted for the previous history of the case to Dr. P. P. Daser, under whose care the patient had been before admission to the German Hospital. There was a doubtful history of syphilis about 1905, but the present illness apparently commenced in November, 1908, with a swelling of the right side of the neck, which increased fairly rapidly in size, though it caused no pain. On February 1, 1909, the patient appeared slightly anemic, but fairly well-nourished, weighing 120 pounds. On the right side of his neck was a movable tumor about the size of an apple, situated beneath the middle third of the sternomastoid muscle and apparently formed by a mass of discrete, enlarged, lymphatic glands. Smaller nodules could be felt lower down in the neck on the same side and some also on the left side. No enlargement of the lymphatic glands elsewhere was detected. A blood film (February 16, 1909) showed slight leukocytosis.

The patient was treated by intramuscular injections of an arsenical preparation, soamin, about every third or fourth day, and at first he seemed to improve. On March 12, 1909, the glandular protrusion on the right side of his neck was scarcely noticeable by sight, though the glands could still be felt. Then he suffered from fever, vomiting, and general malaise (no diarrhea), and kept to his bed for a time. A doctor who attended him thought he had influenza. On April 3, 1909, he looked paler and thinner, weighing only 108 pounds, and the lymphatic glands again had increased in size. Moderate enlargement of the axillary and inguinal lymphatic glands

[1] Read before the Medical Society of London, April 10, 1911.

could likewise be detected. There was no ascites and neither the spleen nor the liver could be felt. Iron and a simple tonic medicine were prescribed. He gained in weight and apparently felt better, but after April he did not come under observation again for a considerable time. He was apparently not taking arsenic. In December, 1909, he wrote that he had a febrile attack, similar to that of March, 1909. This weakened him, but was accompanied or followed by the almost complete disappearance of the swelling on the right side of his neck. Two weeks afterward, however, the lymphatic glands began again to increase in size. When seen on September 26, 1910, he said that for the last five weeks he had been ailing, with loss of appetite, fever, and emaciation. He looked thin and pale; his temperature was 104.6° F., and his pulse 120 to the minute. The lymphatic glands could be felt enlarged, but were smaller and harder than when he was first seen, in February, 1909. The liver and spleen were both enlarged, especially the latter, which was hard and slightly tender to palpation. The urine was free from albumin and sugar. Blood films showed distinct leukopenia.

He was admitted to the German Hospital on September 29, 1910, and there his pyrexia and cachexia continued. The fever was of an irregular septic type, the temperature generally varying between 100° and 103° F. The pulse was frequent and weak. Ascites and jaundice developed in the second half of October, and the jaundice gradually increased in intensity. The feces were pale and the urine contained bilirubin, as in cases of obstructive jaundice.

On November 15, 1910, I noted that he was very feeble, jaundiced, and emaciated, with smooth and uniform enlargement of the spleen and liver. The spleen reached downward to just below the umbilical level. The hepatic dulness commenced above at the sixth rib in the right nipple line, and the lower edge of the liver could be felt at about the umbilical level. The heart and lungs showed nothing special. The tongue and mouth were very dry. The lymphatic glands in the neck could be felt slightly enlarged, but the axillary glands could not be felt at all, and those in the groins were hardly larger than they are in many normal individuals.

Death occurred in a condition of collapse on November 23, 1910. The fever had continued up to the middle of November, but during the last days of life the temperature was usually subnormal and there was a good deal of diarrhea. The urine, when tested about that time, contained 1 per mille albumin. There was little ascites, but a good deal of edema. A few purpuric marks were seen on the abdomen, in lines, as if he had scratched himself, but the jaundice was never accompanied by definite pruritus.

In the hospital, von Pirquet's cutaneous reaction for tuberculosis had given a negative result; so had Widal's reaction. Wassermann's seroreaction for syphilis, performed by Dr. H. R. Dean, at the Lister Institute, was likewise found negative.

A blood examination by Dr. G. Dorner, on September 30, 1910, gave: Hemoglobin, 56 per cent.; red cells, 3,333,330 in the cubic millimeter; color index, 0.86; white cells only, 2480 in the cubic millimeter; no cosinophilia. A differential count of 500 white cells (October 25, 1910) gave: Polymorphonuclear leukocytes, 84 per cent.; small lymphocytes, 3 per cent.; large lymphocytes, 1.7 per cent.; large mononuclears, 7 per cent.; transitionals, 4.3 per cent. Only one nucleated red cell was seen during the count of 500 white cells. The red cells showed anisocytosis and moderate poikilocytosis, as in secondary anemias. On November 12 the hemoglobin was only 35 per cent.; red cells, 1,910,000 in the cubic millimeter; color index, 0.9; white cells, 4124 in the cubic millimeter.

Necropsy and Microscopic Examination. Body much emaciated and jaundiced. The brain and cerebrospinal fluid are not bile stained. The brain weighs 42 ounces and shows slight apparent atrophy of the convolutions. The pericardium contains about 70 c.c. of clear bile-stained serous fluid. On the heart (weight, 9 ounces) are a few pericarditic patches; there is some old thickening of the mitral valve. No atheroselerosis of the aorta or coronary arteries noted. There is chronic indurative pneumonia (as proved by subsequent microscopic examination) of part of the middle and upper lobes of the right lung. Both lungs show hypostatic edema. Pleuritic adhesions are present on both sides. No pulmonary tuberculosis. The peritoneum contains 2400 c.c. of somewhat turbid, bile-stained, ascitic fluid, which is found by microscopic examination to owe its turbidity to the presence of fairly numerous white corpuscles. No evidence of tuberculous peritonitis.

Spleen. Weight, 32 ounces. Uniformly enlarged; rather hard; surface smooth, but showing patches of perisplenitic thickening of the capsule; also one or two scars, which on section are found to be connected with small anemic infarcts. The splenic substance is of a red color and contains numerous small miliary to pea-sized, pale nodules, and a few small hemorrhages.

Liver. Weight, 66 ounces. The surface is smooth and even, with the exception of a little old patchy perihepatitis; it is of greenish color with scattered spots of red. On section, the hepatic substance is found to contain a few pea-sized pale nodules. The red spots beneath the capsule are evidently due to the presence of similar minute nodules, into which hemorrhage has taken place. The common bile duct during life was probably obstructed by a large, chestnut-sized lymphatic gland in the hilum of the liver, but at the necropsy, by firm pressure on the gall-bladder, some bile can be squeezed out through the ducts into the duodenum.

In the kidneys, which weighed together 12 ounces, a little patchy greenish coloration observed in the cortex has been found by subsequent microscopic examination to be probably due to the presence of bile-stained casts in the renal tubules. Nothing special

noted in the suprarenal glands, pancreas, stomach, intestines, thyroid gland (rather large), prostate, testes, urinary bladder, abdominal aorta, or great abdominal veins.

The lymphatic glands are widely affected in the thorax and abdomen. Some of the bronchial glands, which are pigmented, are of about the size of large cherries, and the glands in the posterior mediastinum, close to the spinal column, are likewise enlarged. The mesenteric glands vary from the size of a pea to that of a chestnut, some near the spleen and at the hilum of the liver being specially noticeable. One, as large as a chestnut, in the hilum of the liver is hard, colorless, and almost translucent on section. Several of the lymphatic glands in the neck are as large as a hazel-nut. No matting together of lymphatic glands, as in tuberculosis, observed anywhere.

The bone marrow examined in the shaft of the left humerus is red, with small white nodules in it.

I am greatly indebted to Dr. J. C. G. Ledingham for the following report of the microscopic appearances: A lymphatic gland. The fibrosis of the reticular structure of the gland characteristic of the later stages of Hodgkin's disease (lymphoma granulomatosum) is so far advanced that only small patches of lymphoid tissue remain. Some of these, however, present the typical epithelioid cells and giant cells found in Hodgkin lesions. The giant cells have, as a rule, vesicular nuclei, but in some cases the nuclear chromatin is markedly pyknotic. In the interstices of the fibrotic areas plasma cells are exceedingly numerous, but the great majority show lobing and karyorrhexis of their nuclei. Some giant forms of plasma cells are also present. No necrotic areas are seen on section. Other lymphatic glands examined are characterized mainly by fibrotic changes, typical lymphomata with giant cells being absent. Eosinophilic foci are not found. Many of the perivascular lymph spaces contain large numbers of streptococci. They do not appear in the lumina of the bloodvessels.

Spleen. The structure of the spleen is essentially similar to that of the lymph gland, except that the fibrosis is still further advanced and necrotic areas are present. Normal lymphoid nodes (Malpighian corpuscles) are very scarce, but here and there a typical lymphoma is found with epithelioid and giant cells. The necrotic areas are surrounded by numerous effused blood corpuscles and cells containing hemosiderin are very frequent. Small calcified areas staining well with hematoxylin occur in some of the vessel walls and in the necrotic portions. The sinuses contain large numbers of desquamated endothelial cells.

Liver. The liver nodules resemble the spleen in structure. They have evidently been derived from lymphoid structures in the portal areas. Fibrosis is well advanced, but occasional lymphomatous nodes are left, containing scanty giant cells. The bile

ducts seen in the fibrotic areas show well-marked proliferation of their epithelium, Dr. Ledingham had observed this in one of his own cases.

Bone Marrow. This is essentially myeloid in structure, the great majority of the cells present being neutrophilic and eosinophilic myelocytes. Normoblastic foci are very numerous. The white nodule examined in one of the sections is found to be a necrotic area from which practically all the cellular elements have disappeared.

Sections of liver, spleen, and lymphatic gland, specially stained with methyl-violet, show the presence of a certain amount of amyloid change.

Remarks on the Nature and Diagnosis of Hodgkin's Disease. The present case is, therefore, as the examination after death proves, undoubtedly one of Hodgkin's disease, or, to give this disease some of its synonyms, lymphadenoma, lymphoma granulomatosum, lymphomatosis granulomatosa,[2] Hodgkin's granulomatous lymphoma,[3] Sternberg's lymphatic glandular disease,[4] granulomatosis textus lymphatiei (Typus Paltauf-Sternberg),[5] lymphogranulomatosis (Paltauf-Sternberg),[6] malignant granuloma (granuloma malignum) of the lymphatic apparatus (Benda[7]), malignant granuloma with giant cells,[8] granuloma-like sarcoma of lymphatic glands.[9] The last name fits in best with those cases in which, on microscopic examination after death, the granulomatous growth is found to have invaded bloodvessels,[10] as it did in the case of a man, E. F., aged twenty-seven years, who was under my care in 1905, and whose case I have elsewhere[11] described. Bone erosion from pressure in Hodgkin's disease[12] might clinically suggest a still greater degree of malignancy. The term pseudoleukemia, which has been widely employed in Germany as synonymous with Hodgkin's disease, is said to have been first introduced in 1865 by J. Cohnheim,[13] but it was apparently not intended by him as synonomous with Hodgkin's disease.[14] If the term pseudoleukemia is to be retained in medical literature, it should probably be reserved for those cases of so-

[2] Fraenkel and H. Much, Zeitsch. f. Hygiene, Leipzig, 1911, lxvii, 159; see also Münch. med. Woch., 1910, lvii, 685.

[3] D. Symmers, Publications of Cornell Univ. Med. College: Studies from the Depart. of Path., 1909, vol. ix (separate pagination).

[4] J. Sailer, Philadelphia Med. Jour., 1902, ix, 615, 669; A. Sticker and E. Löwenstein, Centralbl. f. Bacteriol. etc., 1910, lv, 267.

[5] H. Lehndorff, Jahrb. f. Kinderheilkunde, 1908, lxvii, 430.

[6] E. Fabian, Wien. klin. Woch., 1910, xxiii, 1515, and Centralbl. f. allg. Path. u. path. Anat., Jena, 1911, xxii, 145.

[7] Verhandl. d. Deut. pathol. Gesellschaft, Jena, 1904, i, 123.

[8] Schwenkenbecher and Fischer, Abstract in Münch. med. Woch., 1911, lviii, 220.

[9] Dietrich, Deut. med. Woch., 1908, xxxiv, 1188.

[10] Dietrich, Deut. med. Woch., 1908, xxxiv, 1188. Also W. T. Longcope, Bull. Ayer Clin. Lab. of the Pennsylvania Hospital, 1903, No. 1, p. 4; 1906, No. 3, p. 86; 1907, No. 4, p. 18.

[11] F. P. Weber, St. Bartholomew's Hosp. Reports, London, 1908 (for year, 1907), xliii, 81.

[12] W. B. Warrington, Liverpool Medico-Chirurgical Journal, 1911, xxxi, 53.

[13] Virchow's Arch., 1865, xxxiii, 451.

[14] D. Symmers, loc cit.

called lymphosarcomatous, or, better, lymphocytomatous, infiltration of the kidneys, intestines, or other parts of the body, with small, round lymphocyte-like cells, which separate the cellular elements of the infiltrated part without destroying them, thus giving rise to a microscopic picture, exactly resembling that of lymphocythemic infiltration in lymphocythemia or lymphocytic leukemia, but unaccompanied by any lymphocythemic blood changes.[15]

It is highly probable that some of the supposed cutaneous manifestations of Hodgkin's disease have been really lymphocytic nodules in the skin occurring during an early (aleukemic) stage of leukemia. In some cases of Hodgkin's disease a pruriginous eruption develops, which may even progress to a condition of almost universal erythrodermia exfoliativa. The glandular swellings may then be wrongly supposed to be secondary to the cutaneous eruption.[16] In a case that I saw in private practice the itching was present several months before the glandular enlargement was observed.

There are no blood changes characteristic of Hodgkin's disease, but a polymorphonuclear leukocytosis is fairly often met with,[17] probably sometimes as a reaction toward counterinfections of various kinds. A relative increase of lymphocytes, "sign of Pinkus,"[18] probably more often occurs in the cases of pseudoleukemia (lymphocytomatosis or lymphosarcomatosis) to which I have already referred, and it is, of course, found[19] in early, so-called aleukemic stages of lymphocytic leukemia (lymphocythemia). Leukopenia[20] may occur, as proved by the present case, in late stages of Hodgkin's disease, when extensive fibrosis and necrotic changes have taken place in the spleen and lymphatic glandular apparatus of the whole body. Leukopenia must certainly not be regarded as a pathognomonic sign of splenic anemia or Banti's disease, if, indeed, splenic anemia can be regarded as anything more than a symptom complex, due to various causes, and Banti's disease as a late stage of that symptom complex characterized by the presence of cirrhosis of the liver with or without ascites. But to this question I shall return later.

Since Carl Sternberg's well-known paper (1898),[21] "On a peculiar Form of Tuberculosis of the Lymphatic Apparatus Presenting the Clinical Features of Pseudoleukemia," it has been generally acknowledged (1) that cases of tuberculous disease of lymphatic glands are not very rarely met with clinically, resembling Hodgkin's

[15] Fürstenberg and Buchmann, Ziegler's Beiträge z. path. Anat. u. z. allg. Path., 1907, xlii, 447. F. W. Higgs, Proc. Roy. Soc. Med. (Children's Section), 1909, iii, 17. Sterling, quoted by Werdt, vide infra. F. P. Weber, Trans. Path. Soc., London, 1896, xlvii, 117, and Trans. Med. Soc., London, 1909, xxxii, 100, 101. H. Wehland, quoted by Werdt, vide infra. F. von Werdt, Frankfürter Zeitschr. f. Path., 1909, ii, 616; also Banti, quoted by Werdt, loc. cit.

[16] H. D. Rolleston, Brit. Med. Jour., 1909, ii, 852.

[17] E. Fabian, loc cit.

[18] E. Fabian, Deut. med. Woch., 1910, xxxvi, 261.

[19] F. P. Weber, loc. cit., see 11.

[20] E. Fabian, loc. cit.

[21] Zeitschr. f. Heilkunde, 1898, xix, 21.

disease; (2) that tuberculosis occasionally occurs as a superadded infection in cases of Hodgkin's disease. In spite of Musser's[22] and Sailer's[23] summing up, I think that the work of Andrewes,[24] Reed,[25] Simmons,[26] Longcope,[27] Warnecke,[28] Muir,[29] Kidd and Turnbull,[30] and other writers abundantly proves the existence of Hodgkin's disease as a distinct disease or group of diseases with a characteristic morbid histology of its own, although the clinical and postmortem features may sometimes be masked by associated tuberculosis. I have elsewhere[31] discussed this association of Hodgkin's disease with tuberculosis, but I shall here shortly describe another striking example of such association.

The patient, Max L., aged forty-four years, was admitted under my care at the German Hospital on April 22, 1908, and the history of enlarged lymph glands dated from early in 1902. On admission, the spleen and liver could both be felt below the ribs, and there was much enlargement of the lymphatic glands in the neck, armpits, and groins. There were walnut-sized glandular clumps in the axillæ and considerably larger swellings in both inguinal regions, especially on the left side.

There was some ascites. A blood examination by Dr. Chapuis gave: Hemoglobin, 45 per cent.; red cells, 2,500,000 in the cubic millimeter; color index, 0.9. The white cells, especially the polymorphonuclear leukocytes, were greatly increased in number. Treatment by Röntgen rays, which had been previously tried elsewhere, atoxyl, etc., did no permanent good. The patient's general condition varied from time to time, and there were occasional periods of pyrexia. In June, 1908, there was still a large polymorphonuclear leukocytosis present; the white cells numbered 18,550 in the cubic millimeter of blood. A right-sided pleuritic effusion needed occasional tapping in September and October, 1908. In November, 1908, some diminution was noted in the size of the lymphatic glands in the right groin. There was still much leukocytosis, 28,000 white cells in the cubic millimeter of blood. In 1909 the patient suffered from increasing feebleness, emaciation, and dropsy, and died on February 21, 1909. At the postmortem examination and subsequent microscopic examination tuberculous lesions were found in the lungs, liver, spleen, and lymphatic glands, and a necrotic change, probably of tuberculous origin, was present in one of some whitish nodules from the bone marrow, which was red

[22] Trans. Assoc. Amer. Phys., 1901, xvi, 638.

[23] J. Sailer, loc. cit.

[24] Trans. Path. Soc., London, 1902, liii, 305.

[25] Johns Hopkins Hosp. Reports, 1902, x, 133.

[26] Jour. Med. Research, 1903, ix, 378.

[27] W. T. Longcope, loc. cit.

[28] Mitteil. a. d. Grenzgebiet. d. Med. u. Chir., Jena, 1905, xiv, 275.

[29] Glasgow Med. Jour., 1905, lxiv, 161.

[30] Arch. Path. Inst., London Hospital, 1908, ii, 130 to 155.

[31] F. P. Weber, loc. cit., sec. 11; Lancet, London, 1904, i, 924 to 928. (Contains references to older literature on the relation of tuberculosis to Hodgkin's disease.)

in color, of the shaft of the left humerus. But in the largest inguinal gland, kindly examined by Dr. J. C. G. Ledingham, the characteristic features of Hodgkin's disease were detected. It is by the way, perhaps, worth mentioning, that Calmette's ophthalmoreaction for tuberculosis had been tried in May, 1908, with a negative result.

The necrotic and lardaceous changes found after death in the viscera of some cases of Hodgkin's disease, as in the case of H. A., specially under consideration, by their resemblance to changes found in cases of syphilis, tuberculosis, and other microbic diseases, suggest that the exciting cause of Hodgkin's disease is a microbic infection of some kind. Similarly, the fibrotic and cicatricial changes which form so conspicuous a feature in the pathological histology of late cases of Hodgkin's disease are probably analogous to the conservative and limiting fibrosis of chronic tuberculous and tertiary syphilitic lesions. The microbic theory is likewise supported by the occasional occurrence of very acute cases, to examples of which I have elsewhere[32] drawn attention. Acute cases have also quite recently been described by A. T. Wilkinson,[33] J. Mitchell Clarke,[34] and Hirschfeld and Isaac.[35] But though the cause of Hodgkin's disease is almost certainly microbic, attempts at inoculation and cultivation have repeatedly given negative results. Pröscher and White,[36] indeed, in 1907, reported that, by the Levaditi and Giemsa methods of staining, they had succeeded in detecting spirochetes of some kind in human lymphadenomatous glands, but their results have not been confirmed by other investigators. Neither is the recent paper by Eug. Fraenkel and H. Much,[37] of Hamburg, very convincing. These observers claim that Hodgkin's disease, which they call lymphomatosis granulomatosa, is produced by granule-like bacteria (granules of Much), which are intimately allied to, if not actually a variety of, the Bacillus tuberculosis, and which are said to be stained by an intensified Gram method, and though not "acid-fast," to be resistant to antiformin. Here, I may mention that Sticker and Löwenstein,[38] who think that Hodgkin's disease is probably caused by bovine tubercle bacilli, claim that, by inoculation of material from cases of Hodgkin's disease in man, they have succeeded in producing a granulomatous tissue in guinea-pigs, which, although apparently free from tubercles and tubercle bacilli, nevertheless is capable of setting up obvious tuberculosis when it is reinoculated into other guinea-pigs. Obviously such results need much confirmation before acceptance.

[32] F. P. Weber, loc. cit., see 11.
[33] Manchester Path. Soc., March 10, 1909; also Lancet, 1909, i, 920.
[34] Jour. of Path. and Bact., Cambridge, 1908, xii i,92.
[35] Med. Klinik, 1907, iii, 1580.
[36] Jour. Amer. Med. Assoc., 1907, xlix, 774, 1115; also Münch. med. Woch., 1907, liv, 1868.
[37] Loc. cit.
[38] Loc. cit.

In true Hodgkin's disease the lymphatic glands of some one region of the body are much more enlarged at first than the others, as if they constituted the primary focus or centre of the disease.[39] Not rarely, as in the present case of H. A., those on one side of the neck are chiefly affected at first; sometimes a group of retroperitoneal glands seems to be primarily involved;[40] in a case under my care in 1908 the disease commenced in the mediastinum,[41] and so it did in a boy, aged four years, whose case is one of those described by Kidd and Turnbull;[42] Douglas Symmers[43] has described a case which he regards as one of "primary Hodgkin's disease of the spleen." However, Symmers' case is by no means conclusive. The patient, a woman, aged eighteen years, died on the day following the operation of splenectomy, and the spleen was examined microscopically, but no postmortem examination of the other abdominal and thoracic contents was obtained. I believe that the disease, when it is localized in the mediastinum, as it was in a case of mine, to which I have just referred,[44] may give rise to a regular tumor-mass, not merely a conglomeration of lymphatic glands.

In the present cases (H. A.), as doubtless in several other cases, the superficial lymphatic glands, which at first formed a prominent tumor on one side of the neck, shrivelled up during the course of the disease so as to become hardly noticeable. The disease superficially appeared to be in process of cure, but in reality, the lymphatic glands in the thoracic and abdominal cavities and the lymphatic tissue of the spleen were becoming gravely affected. Something of the same kind is doubtless what happens in many cases in which more or less complete cure is supposed to have been affected by arsenical medication or by the action of Röntgen rays. As the disease progresses, the lesions of Hodgkin's disease tend to become more and more fibrotic and to lose their characteristic microscopic features. This is well illustrated by the present case (H. A.), and by one or two unpublished cases of which Dr. Ledingham has told me. Probably in most cases a counterinfection of some kind takes place at the end, and in the case of H. A. the presence of streptococci in the perivascular lymph spaces of lymphatic glands affords evidence of such a terminal infection.

With regard to clinical diagnosis in the present case, the negative results of Wassermann's seroreaction for syphilis and von Pirquet's cutireaction for tuberculosis were of some value, and leukemia was completely negatived by the blood picture. Hodgkin's disease may

[39] F. P. Weber, loc. cit., sec 11.
[40] W. T. Longcope, loc. cit. F. Warnecke, loc. cit.
[41] F. P. Weber and J. C. G. Ledingham, Proc. Roy. Soc. Med. (Clinical Section), 1909, ii, 66.
[42] Loc. cit.
[43] Loc. cit.
[44] Weber and Ledingham, loc. cit.

perhaps be simulated[45] by malignant disease of abdominal viscera (suprarenals) with secondary infiltration of lymphatic glands in the neck, but had there been any such abdominal malignant disease in the present case, one would have expected enlargement of the inguinal as well as of the cervical glands to have ultimately occurred; moreover, the diminution and almost complete disappearance of the cervical swelling would hardly have been likely, had it been due to carcinomatous infiltration. H. D. Rolleston[46] and others draw attention to the possibility of cases with splenic enlargement and pyrexia, suggesting a diagnosis of malaria or enteric fever, and, indeed, in the present case it was thought advisable to try Widal's reaction, but the result was negative.

In only a few cases of Hodgkin's disease does the patient's temperature chart help at all in the diagnosis. When there is any fever, it is mostly of an irregular kind with a moderate evening rise, but occasionally a long, regularly recurrent, periodic type of fever[47] is met with, the chronic relapsing pyrexia of Hodgkin's disease, which has been called the "Pel-Ebstein symptom," owing to the writings of Pel[48] and Ebstein,[49] in 1887. Of this, perhaps the most remarkable example in existence is an eight month's chart, recently recorded by C. H. Melland.[50] Such cases have even been labelled "Ebstein's disease." Less regular recurrent "pyrexial crises" are of rather commoner occurrence. During the pyrexial periods the superficial lymphatic glands are sometimes observed to swell, but they occasionally seem to diminish rather than increase in size, as in the case of Hodgkin's disease shown by Dr. J. Porter Parkinson before the Medical Society of London on March 27, 1911.

Wherever possible, the diagnosis of Hodgkin's disease should be confirmed at an early stage of the excision and microscopic examination of one of the enlarged lymph glands. Without the help of a biopsy it is by no means always so easy, as some probably suppose, to distinguish Hodgkin's disease from chronic tuberculous or syphilitic enlargement of lymph glands. Many persons are doubtless alive and well today who would have been long since dead had the diagnosis of Hodgkin's disease pronounced on them been the correct one. Mistaken diagnoses in syphilitic and, especially, tuberculous cases doubtless account for many of the supposed cures of Hodgkin's disease. But that arsenical therapy (Fowler's solution, arsacetin, etc.) and the application of Röntgen rays can be of real use in many genuine cases of Hodgkin's disease there can scarcely be a doubt, even if a permanent cure cannot be effected. This consider-

[45] H. D. Rolleston, personal communication.

[46] Practitioner, 1911, lxxxvi, 496.

[47] F. de H. Hall, Practitioner, 1911, lxxxvi, 473. L. Hofbauer, Wien. med. Woch., 1905, lv, 86. J. H. Musser, loc. cit. F. Taylor, Guy's Hosp. Reports, 1906, lx, 1.

[48] Berliner klin. Woch., 1887, xxiv, 641.

[49] Ibid., 565.

[50] Edinburgh Med. Jour., 1911, New Series, vi, 156 to 164, Chart 1.

ation makes it very important that the diagnosis should be made as certain as possible by the help of a biopsy, so that arsenical medication may be carefully and methodically pushed, and *x*-rays perhaps also made use of. Mistakes in diagnosis in regard to the question of Hodgkin's disease have, however, sometimes, it must be admitted, been made, even after a biopsy and all other available methods. I may here mention that the great difference in regard to the ordinary progress of the disease between tuberculous lymph glands and the lymph glands of Hodgkin's disease furnishes another argument against the view that Hodgkin's disease is caused by any variety of the bacillus tuberculosis.[51]

A point of extreme clinical interest in the present case was the development of splenic enlargement and ascites, which, together with the subsidence and practical disappearance of the superficial lymphatic glandular tumors and the association of marked leukopenia with the anemia, produced the clinical picture of Banti's disease, that is to say, the stage of splenic anemia characterized by hepatic cirrhosis and ascites. So great, indeed, was the clinical resemblance, that the diagnosis of Banti's disease was actually arrived at by medical men who had not had an opportunity of seeing the case at an earlier period when the superficial glandular swelling in the neck was the most marked feature. The leukopenia may have been a result of the fibrotic and necrotic changes which involved so large a proportion of the lymphadenoid apparatus of the body.

Granting that there is a definite disease which may be termed splenic anemia, or, in its later stages, Banti's disease, I will now shortly consider a few of the conditions which may clinically simulate it.

Remarks on Various Cases Presenting the Clinical Picture of Splenic Anemia (Banti's Disease). Hodgkin's disease, or lymphadenoma, "with splenic predominance," as seen in the late stages of H. A., the present case, that is to say, a kind of splenic type of Hodgkin's disease, has been likewise called the Griesinger or lymphadenomatous type of splenic anemia, but Griesinger's original case, described by his pupil, Gretsel,[52] in 1866, was apparently not a certain one. The patient was a female child, aged only ten months, with great enlargement of the spleen and less enlargement of the liver, moderate rickets, and no leukemic blood changes. At the necropsy the lymphatic glands of the mesentery and retroperitoneal region were found enlarged, and Cohnheim, who examined the spleen microscopically, reported that it showed only hyperplasia of its normal constituents. There was a kind of fibrosis in the liver

[51] Fraenkel and Much, loc. cit. J. H. Musser, loc. cit. J. Sailer, loc. cit. G. Sternberg, loc. cit. Sticker and Löwenstein, loc. cit.

[52] Berl. klin. Woch., 1866, iii, 212.

and kidneys. Griesinger's case cannot, therefore, with certainty be claimed as one of Hodgkin's disease in the modern sense of the term.

Leukopenia occurs in various conditions other than splenic anemia, conditions in which the spleen is chronically enlarged and has undergone extensive fibrotic or necrotic changes, and in which probably a great portion of the total lymphadenoid apparatus of the body is involved. I have already referred to the occurrence of leukopenia in the later stages of Hodgkin's disease. Leukopenia may occur in chronic malarial and syphilitic[53] disease of the spleen and liver.[54] Thus, S. S. Cohen and Rosenberger[55] drew attention to the occurrence of blood changes resembling those of Banti's disease in a case of splenomegaly apparently due to malaria. The connection of some cases of supposed Banti's disease with congenital or acquired syphilis has been suggested by Marchand[56] and others.[57]

Among hospital patients occasionally met with in London are sailors and various persons who give a history of having had malaria and having repeatedly visited or resided in hot climates, and who suffer from anemia with chronic splenomegaly, enlargement of the liver, doubtless a form of hypertrophic cirrhosis, and sometimes marked leukopenia.

In a man, M. C., aged twenty-five years, who had spent twelve years of his life in Jerusalem, where he had suffered a good deal from malaria, there was much enlargement of the spleen and considerable enlargement of the liver, slight jaundice, and anemia. While he was under my care at the German Hospital the number of his white corpuscles varied from 1200 to 4200 in the cubic millimeter of blood. His general health and appearance improved markedly and the jaundice disappeared.

A soldier, W. V., aged twenty-six years, was under my observation, in 1903, for enlargement of the spleen and liver, emaciation, anemia, slight albuminuria, and oozing of blood from the gums. He had lived for six years in India, where he had had attacks of enteric fever and malaria. He had been accustomed to a good deal of alcohol. When I saw him no malarial parasites were found in the blood and there was no leukemia. His white corpuscles varied between 3748 and 7180 in the cubic millimeter of blood. I heard that he died of "syncope" in September, 1903, and that there was a postmortem examination, but I could ascertain little more than that the spleen weighed $6\frac{1}{2}$ pounds, the liver 10 pounds, and the heart 15 ounces.

[53] Leukopenia may likewise occur in splenomegaly due to primary tuberculosis of the spleen. In such a case described by P. Albrecht at a Viennese Medical Society (Wiener med. Woch., 1908, lviii, 2854) the white cells were counted at 3000 in the cubic millimeter of blood before the operation of splenectomy.

[54] L. d'Amato, Zeit. f. klin. Med., Berlin, 1905, lvii, 261.

[55] Amer. Jour. Med. Sci., Philadelphia, 1904, cxxviii, 271.

[56] Münch. med. Woch., 1903, l, 463.

[57] W. Schmidt, Münch. med. Woch., 1911, lviii, 625.

In apparently similar cases the pathology and etiology may sometimes be very complicated. An example of this is the case of W. S., a fireman on a steamship, aged forty-two years, whom I showed to the Medical Society of London on April 8, 1907.[58] He gave a history of having taken a good deal of alcohol, of having contracted a chancre ten years ago, and of having suffered from fever, apparently malaria. He was anemic and the size of his spleen and liver was enormous. When at the German Hospital, in London, his white corpuscle count varied from 4160 to 10,000 in the cubic millimeter of blood. No malarial parasites were found, and some blood films from the liver were kindly examined by Captain W. G. Liston, I.M.S., for kala-azar parasites,[59] but with negative result. The patient afterwards went to a hospital at Stockholm, where he had to be tapped for ascites. A blood count made at Stockholm gave: Red cells, 3,500,000 in the cubic millimeter; white cells, 4300 in the cubic millimeter; polymorphonuclears, 70 per cent.; large lymphocytes, 16 per cent.; small lymphocytes, 12 per cent.; eosinophiles, 2 per cent.; hemoglobin, by von Fleischl's method, 50 per cent. He died in the hospital on May 19, 1908, and the Medical Superintendent, Dr. G. D. Wilkens, who very kindly wrote to me about the case, summed up the changes found at the postmortem examinations as follows: Fibrous pericarditis, with complete adhesion of the two surfaces; chronic fibrous myocarditis; acute pneumonia of the lower lobe of the right lung; hepatic cirrhosis; splenomegaly with fibrous induration and spots of pigmentation, possibly left by old malaria; tuberculous peritonitis; tuberculosis of the bronchial and periportal lymphatic glands.

A very interesting case of chronic malignant endocarditis simulating splenic anemia[60] came under my notice in 1909. The patient, G. W., was a sailor, aged twenty-eight years, who had contracted malaria in the Straits Settlements about four years previously. When seen in London, however, he presented no signs of active malaria, and had already been treated at several London hospitals, where apparently the diagnosis of splenic anemia had been made. At the German Hospital he was extremely pale, weak, and wasted, and there was a tendency to bleeding from the gums. His spleen extended downward into the inguinal region, and his liver was likewise enlarged and hard. His legs were pigmented as a result of a chronic petechial eruption, and there were a few minute hemorrhages in the skin of the arms and trunk, in the conjunctivæ, and in the retinæ. There was great anemia with leukopenia. Red cells,

[58] F. P. Weber, Trans. Med. Soc., London, 1907, xxx, 393.

[59] Cf. cases of hepatic cirrhosis due to the protozoal parasite of kala-azar, described by L. Rogers (Ann. Trop. Med. and Parasitol., Liverpool, 1908, ii, 147); also the cases of infantile splenomegaly with anemia, due to Leishman parasites, described by Nicolle, Jemma, Pianese, Gabbi, Feletti, Cannata, and others.

[60] F. P. Weber, Trans. Med. Soc., London, 1910, xxxiii, 83.

1,700,000 in the cubic millimeter of blood; white cells, 1200 to 1900 in the cubic millimeter; hemoglobin, 30 to 35 per cent. The heart was somewhat enlarged and there was a systolic apical murmur. The necropsy showed the presenee of chronic malignant endocarditis, and a microscopic examination by Dr. J. C. G. Ledingham of pieces of the spleen, liver, kidney, and bone marrow from the shaft of the humerus, showed, in all four organs, as their most conspicuous pathological histological feature, a plasma eell development with the elaboration of new fibroblastic tissue.

Perhaps, after all, in the present state of our knowledge, splenic anemia, with its later stage, known as Banti's disease, is best looked upon as a symptom group, which may be set up by various pathogenic agencies, the nature of some of which is known, though that of others has not yet been discovered.

In quite a considerable number of cases presenting during life the clinieal features of splenic anemia, old thrombotic obstruction of the splenic and portal veins, with sometimes more extensive recent thrombosis as well, has been discovered after death. For examples of that kind we could refer to the published cases of Dock and Warthin,[61] 1904, Oettinger and Fiessinger,[62] 1907, Edens,[63] 1907, F. Dévé,[64] 1908, and several others; occasionally the splenic artery has been found diseased. In some of these cases the splenomegaly was doubtless secondary to the obstruction in the splenic and portal veins, but in other cases the vaseular disease may have been secondary to a toxemia of splenic origin.

Cases of biliary cirrhosis of the liver, Hanot's type, with splenomegaly,[65] are, owing to the chronic jaundice, seldom likely to be diagnostieated as cases of splenic anemia. The Gaucher type of primary splenomegaly[66] is scarcely ever met with. But there are certain cases of congenital or acquired chronic acholuric, so-called hemolytic jaundice, with splenomegaly and anemia,[67] which might, owing to the temporary or permanent absence of obvious clinical jaundice, be mistakenly labelled as examples of splenic anemia. Such cases might be headed splenomegalic anemia or splenomegalic hemolytic anemia, acquired or congenital, to avoid the confusion with splenic anemia.[68] In a paper,[69] with Dr. Dorner on "Four

[61] Amer. Jour. Med. Sci., Philadelphia, 1904, cxxvii, 24.

[62] Revue de Méd., Paris, 1907, xxvii, 1109.

[63] Mitteil. a. d. Grenzgebieten d. Med. u. Chir., Jena, 1907, xviii, 59.

[64] Normandie Médicale, March 1, 1908; abstract in Arch. des Maladies du Cœur, etc., Paris 1908, i, 606.

[65] F. P. Weber, Trans. Path. Soc., London, 1903, liv, 103.

[66] Weber and Dorner, vide infra.

[67] F. P. Weber, Amer. Jour. Med. Sci., Philadelphia, 1909, cxxxviii, 24; F. P. Weber and G. Dorner, Lancet, London, 1910, i, 227.

[68] Armand-Delille, Soc. de Pédiatrie, Paris, June 23, 1910. Armand-Delille and Feuillée, Soc. méd. des Hôpitaux de Paris, February 2, 1909. Chauffard and Troisier, Soc. Méd. des Hôpitaux de Paris, February 19, 1909. R. Hutchison, Case of Splenomegaly, shown at the Clinical Section of the Royal Society of Medicine, March 10, 1911.

[69] Weber and Dorner, loc. cit.

Cases of Congenital Acholuric Jaundice in One Family," we wrote: "It is highly probable that in some cases of the disease the jaundice, at all events, obvious jaundice, may be intermittent instead of remittent, that is, that for a time at least jaundice may be apparently absent, though the splenomegaly and characteristic blood features of the disease are present. Such cases might be clinically termed cases of splenomegalic anæmia. . . . In other words, it appears almost certain that a form of splenomegalic anæmia without jaundice may occur, although, perhaps, only temporarily, as an incomplete form of the chronic splenomegalic acholuric jaundice, of which the family in question affords complete examples."

In conclusion, I must specially thank Dr. Daser for his information on the early history of the patient H. A., Dr. Dorner for his help in the examination of the same case at the German Hospital, and Dr. Ledingham for his kind report on its pathological histology.